specimens from localized and metastatic prostate cancer, benign prostatic hypertrophy, normal prostates, and certain prostatic cultured cell lines. In addition a monoclonal antibody of this invention recognizes a reactive epitope that is in a soluble form in sera of patients with prostatic cancer.--

A4 Cont'd

REMARKS

The specification and claims have been amended to correct obvious editorial and typographical errors.

The Abstract has been amended to particularly point out and distinguish the specific features of Applicant's claimed invention. As described throughout the specification and particularly on page 14 at line 31 through page 15, line 5, monoclonal antibody 7E11-C5 binds to an epitope from specimens of normal prostatic epithelium, benign prostatic hyperplasia, localized and metastatic prostate cancer and certain prostatic cultured cell lines. These specimens thus represent normal, neoplastic and malignant prostatic epithelial cells. Moreover, as described in § 6.8 at pages 39 through 49, monoclonal antibody 7E11-C5 also recognizes a soluble reactive epitope in sera of patients with prostatic carcinoma.

The claims have been amended to particularly point out and distinctly claim the subject matter Applicant regards as his invention in accord with Examiner's suggestions. All claims as amended are fully supported by the specification and claims as originally filed.

The Examiner has required restriction under 35 U.S.C. § 121 to one of the following inventions:

Group I, claims 1-31 drawn to monoclonal antibodies, processes for producing monoclonal antibodies, hybridomas and general methods for detecting prostate carcinomas;

Group II, Claims 32-39, drawn to a non-invasive competitive binding immunosorbent method for detecting prostatic carcinoma;

Group III, Claims 40 and 42, drawn to passive immunotherapy methods; and

Group IV, Claim 41, drawn to an immunotherapy method using a cytotoxic conjugate.

If Group I is elected, further election of a single disclosed species has been required. Examiner has indicated that the species disclosed are:

I, a monoclonal antibody with the characteristics of 7E11-C5 and corresponding hybridoma; and

II, a monoclonal antibody with the characteristics of 9H10-A4 and corresponding hybridoma.

On January 26, 1990, Dr. Karen Lowney as representative of Applicant made a provisional election, with traverse, by telephone to prosecute the invention of Group I and species I including claims 1-24, 26 and 28-31 in this application. Applicant affirms the election of Group I and species I including claims 1-24, 26 and 28-31 without traverse. Applicant reserves the right to prosecute the subject matter of the non-elected claims in a subsequent divisional application.

Examiner has objected to the figures because of the quality of Figure 2 and has requested that each Figure be numerically labeled.

Applicant encloses with this amendment new Figures 1-3 which have been numerically labeled. New Figure 2 allows evaluation of the staining pattern of monoclonal antibody 7E11-C5. Accordingly, Applicant respectfully requests that the objection to the figures be withdrawn.

The Examiner has objected to the Abstract of the present application. In this response, Applicant has amended the abstract to clarify the confusion caused by an editorial omission in the abstract. Applicant corrects the abstract to identify the determinants recognized by the antibodies of the invention as being present on normal, neoplastic and malignant prostatic cells as disclosed in the specification. In response to Examiner's erroneous statement that the diagnostic and therapeutic uses of the monoclonal antibodies are not supported in the specification, Applicant notes that the therapeutic and diagnostic utility of the monoclonal antibodies of the invention are disclosed throughout the specification but are particularly described in § 5.7 at pages 19-20, in § 5.8 at pages 21-24, in § 6.7 at pages 33-34 and 36-37, and in § 6.8 at pages 39-49. Therefore, Applicant's statement in the abstract that "the monoclonal antibodies, specifically, 7E11 monoclonal antibodies, can be used diagnostically and therapeutically" at page 58 lines 9-11 is entirely proper.

Examiner has objected to claims 10, 11 and 28 under 37 C.F.R. § 1.75(c) as being in improper form. Claims 10, 11 and 28 have been amended herein to depend upon independent claim 1 or 2 and thus obviate Examiner's objection. Applicant respectfully requests that this objection be withdrawn.

1. Objections To The Specification and Rejections of Claims Under 35 U.S.C. § 112

Examiner has rejected claims 1-4, 7, 8, 11 and 14 under 35 U.S.C. § 112 second paragraph as indefinite. Examiner states that the phrase "is reactive" in claim 1 is not clear and suggests substitution of "is reactive with" by "specifically binds" to. As suggested by Examiner, claim 1 has been amended to recite that the antibody "specifically binds to" the relevant epitope.

Claim 2 has been amended to obviate Examiner's rejection of the term "immunologically staining". Applicant's amendment more particularly points out and distinctly claims the subject invention by indicating that, upon binding to prostatic epithelium, the monoclonal antibody can be detected by immunological staining methods.

Examiner has stated that claim 3 is indefinite for specifying the exact subcellular localization of binding and in indicating which prostatic cell types are bound by the antibody. Applicant has amended claim 3 to more particularly point out and distinctly claim one aspect of Applicant's invention, i.e., a monoclonal antibody that binds specifically to an epitope present on a membrane associated antigen of human prostatic cancer epithelium and normal prostatic epithelium which binding can be detected by an immunological staining method that intensely stains prostatic cancer cells with a small degree of heterogeneity and weakly stains normal prostatic epithelial cells and nonmalignant prostatic ductal epithelium.

Examiner has rejected claims 4 and 11 as indefinite in the recitation of "other carcinomas". Applicant has amended claim 4 (and 11 dependent thereon) to more particularly point out the subject matter that Applicant regards as his invention. One embodiment of his invention encompasses

monoclonal antibodies which react with a prostate specific epitope, where the antibodies result from a process comprising a) immunization of a mammal with LNCaP cells and/or components thereof and b) forming hybridomas using the immunized mammalian cells. In demonstrating the specificity of the binding of the monoclonal antibodies, Applicant has tested a variety of non-prostatic cancers as shown in Table I at page 34 and Table 2 at page 37 of the specification. As demonstrated, the monoclonal antibodies of the invention are highly specific for prostatic cancers and fail to recognize any other non-prostatic cancerous cells. The data presented in Tables I and 2 clearly and convincingly evidence the unique specificity of the antibodies as presently claimed.

Examiner has rejected Claim 7 as indefinite because "the recitation of an animal immunized with a 'metastatic lesion'" is "not clear as to what the term encompasses." Applicant has amended claim 7 to more particularly point out and distinctly claim what Applicant regards as his invention. As amended, claim 7 encompasses cells and tissues directly obtained from an individual as well as cultured cell lines established from metastic lesions of prostatic carcinoma.

Examiner has rejected claim 8 for failure of proper antecedent basis in claim 7 from which it depends. Additionally, the Examiner has stated that claim 8 is unclear because of the phrase "derived from" and suggests substitution of that phrase by "isolated from" or "originating from." Claim 7 has been amended to recite "human prostatic carcinoma cells" which provides the proper antecedent basis for claim 8. Claim 8 has also been amended to substitute "originating from" for "are derived" as suggested by Examiner.

Examiner has rejected claim 14 as indefinite for recitation of "a membrane" rather than a "membrane enriched fraction". Applicant has amended claim 14 to recite "a membrane fraction" as suggested by Examiner.

Claim 18 has been amended to recite "cells" in line 5 as suggested by Examiner.

Claim 24 has been amended to recite --ATCC Designation HB 10494-- as requested by Examiner.

In view of the above-detailed amendments, it is respectfully submitted that the rejection of claims 1-4, 7, 8, 11 and 14 under § 112, second paragraph has been obviated and should be withdrawn.

The Examiner has objected to the specification under 35 U.S.C. § 112, first paragraph, for failing to support a monoclonal antibody as claimed in claim 1, that is specific for a membrane-associated prostatic epithelial antigen. Examiner notes that the specification describes two, potentially related, reactive components with which monoclonal antibody 7E11-C5 binds: the first is a membrane-associated non-soluble prostatic epithelial antigen, and the second is a soluble component found in the serum of patients with prostatic carcinoma. To avoid confusion and particularly point out and distinctly claim Applicant's invention, Applicant has amended claim 1 (and also claims 16, 21, 23, 32 and 33) to delete the term "non-secretory". In light of such amendment, the present claims and the specification as originally filed consistently are directed to the unique, novel monoclonal antibodies discovered by Applicant. In view of such amendments, attorneys for Applicant submit that this objection should be withdrawn.

Examiner has objected to the specification and rejected

claims 1-24, 26 and 28-31 under 35 U.S.C. § 112, first paragraph, for failing to provide complete evidence of the deposit of the biological material, i.e. hybridoma cell line 7E11-C5.

Applicant herein provides the Declaration of S. Leslie Misrock which states that as attorney for Applicant, he deposited hybridoma 7E11C with the ATCC which deposit was designated as HB 10494. He further declares the deposited material is the same material identified in the subject application. Moreover, he assures the United States Patent and Trademark Office and the public that a) all restrictions on the availability to the public of the culture referred to in paragraph 2 will be irrevocably removed upon issuance of a United States patent of which such culture is the subject; (b) each culture will be maintained for a period of at least five years after the most recent request for the furnishing of a sample of the deposited culture was received by the ATCC and, in any case for a period of at least 30 years after the date of deposit; (c) should the deposit become non-viable it will be replaced by the Applicant; and (d) access to the culture will be available to the Commissioner during the pendency of the patent application or to one determined by the Commissioner to be entitled to such culture under 37 C.F.R. § 1.14 and 35 U.S.C. § 122. Attached to the Declaration as Exhibit A is a copy of the International Form in accordance with the requirements of the Budapest Treaty On The International Recognition of The Deposit Of Microorganisms For The Purposes of Patent Procedure. Exhibit A indicates that Hybridoma 7E11C of ATCC Designation HB 10494 has been accepted and the culture was viable after testing. Also attached to the Declaration as Exhibit B is the original Safe Deposit Agreement between the ATCC and Cytogen Corp. for

the initial deposits of hybridoma 7E11C as CYT-351, S.D. No. 1307 and hybridoma 9H10-A4 as CYT-368, S.D. No. 1308, which deposits were not in compliance with the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure. The specification has been amended to indicate the appropriate ATCC designation on page 49 for both hybridoma cell cultures.

In light of the above remarks and the Declaration of S. Leslie Misrock, attorneys for Applicant submit that this objection and rejection of claims 1-24, 26, and 28-31 has been obviated and should be withdrawn.

2. Rejection of Claims 1-24, 26 and 28-31 Under 35 U.S.C. § 102(a)

Examiner has rejected claims 1-24, 26, and 28-31 under 35 U.S.C. § 102(a) as being anticipated by Horoszewicz et al., Anticancer Research 7: 927 (1987) [hereinafter "Horoszewicz et al."]. Examiner states that the reference presents an ambiquity with respect to inventorship because Horoszewicz et al. is co-authored by E. Kawinski and G. Murphy as well as J. Horoszewicz but the invention has only a single inventor. Examiner further states that there is an ambiquity in inventorship because on page 928 Horoszewicz et al. attributes the production of hybridoma 7E11-C5 to S. Leong.

Attorneys for Applicant provide Examiner with a Declaration of Dr. Julius Horoszewicz, the sole inventor and Applicant, which resolves the ambiquity. As affirmed therein, Dr. Horoszewicz is the inventor of the invention claimed in this application and, to the extent that the invention is described in Horoszewicz et al., he is the inventor of the subject matter as described in the reference. Dr. Horoszewicz states that he conceived of the monoclonal antibodies and the process for obtaining them using

immunization with LNCaP components and/or cells. Dr. Horoszewicz provided S. Leong with the antigen used for immunization and provided instructions, to S. Leong and other technical personnel in his laboratory, for producing, analyzing and characterizing the different hybridoma cultures and the resulting antibodies. The conception of such cell cultures or monoclonal antibodies and the conception of their relationship to prostatic cancer was Dr. Horoszewicz' conception. It was not the conception of Dr. S. Leong, Dr. E. Kawinski or Dr. G. Murphy. As such, Dr. Horoszewicz is the sole inventor of the invention of the subject application.

In light of the Declaration of Dr. Horoszewicz, attorneys for Applicant submit that a satisfactory showing that he is the sole inventor of the claimed subject matter has been provided. In re Katz, 215 U.S.P.Q. 14 (C.C.P.A. 1982). In view of the foregoing, attorneys for Applicant submit that this rejection has been overcome and that withdrawal of the rejection of claims 1-24, 26 and 28-31 under 35 U.S.C. § 102(a) is appropriate.

3. Rejections of Claims Under 35 U.S.C. § 102(b) and/or § 103

Examiner has rejected claims 1-3, 10, 11, 20, 28, 29 and 31 as being unpatentable under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, obvious under 35 U.S.C. § 103 over Frankel et al., Proc. Nat'l. Acad. Sci. USA 79: 903 (1982) [hereinafter "Frankel"].

Examiner has rejected claims 1-3, 5, 7-11, 16, 17, 19-23, 28, 29 and 31 as being unpatentable under 35 U.S.C. § 102(b) as anticipated by, or in the alternative, obvious under 35 U.S.C. § 103, over Webb et al., Cancer Immunol. Immunother. 17: 7 (1984) [hereinafter "Webb"].

Examiner has rejected claims 1-6, 10-14, 20-22, 28, 29 and 30 as being unpatentable under 35 U.S.C. § 102(b) as anticipated by, or in the alternative, obvious under 35 U.S.C. § 103, over Finstad et al., Proc. Nat'l. Acad. Sci USA 82: 2955 (1985) [hereinafter "Finstad"].

Examiner has rejected claims 1-24, 26 and 28-31 as being unpatentable under 35 U.S.C. § 103 over Campbell, "Monoclonal Antibody Technology" in Laboratory Techniques in Biochemistry and Molecular Biology, Vol. 13, Ed. Burdon et al., Elsevier, Amsterdam at pages 1-85 [hereinafter "Campbell"] in view of Wright et al., Cancer Research 43: 5509 (1983) [hereinafter "Wright"] in view of Webb and Frankel.

Applicant respectfully disagrees with Examiner's rejections under 35 U.S.C. § 102 and § 103 and for reasons detailed below submit that neither the monoclonal antibodies specific for prostatic antigens nor the process for making them are in any way anticipated or made obvious by the cited references.

3.1. The Cited References

3.1.1. Frankel

Frankel describes the production of monoclonal antibodies generated following immunization of mice using preparations of membrane-enriched cell extract (stored at -70°C) from frozen non-malignant benign prostatic hyperplasia tissue obtained from urethral resections of human prostates. As described in the Abstract at page 903, the resulting monoclonal antibodies each had considerable organ, tissue or cellular cross-reactivity when specificities were tested. For example, monoclonal antobodies mab 35 and 24 both recognize prostate epithelium, but mab 35 also reacts with kidney and mab 24 also reacts with salivary gland (see p.

904, col. 2). Both monoclonal antibodies also reacts with breast carcinoma. The authors also state "Most of the antibodies showed an irregular staining of apparent lymph node dendritic cells and Hassal's corpuscles in the thymus."

3.1.2. Webb

Webb discloses, on p. 9 at col. 1, a process for generating mab α-Pro 13 using immunization with a prostate tumor cell mixture containing equal cell portions of PC-3, DU-145 and LNCaP cells. The resulting monoclonal antibody α-Pro 13 in the author's own words "exhibits high, but not absolute, specificity for prostate tissue." The reference indicates that the α-Pro 13 monoclonal antibody shows a preference for prostate ductal epithelium but cross-reacts with blood vessel endothelium (see summary at p. 7). As described on pages 9-11, mab α-Pro 13 has no reactivity with LNCaP cells. Any useful diagnostic or therapeutic utility is precluded because mab α-Pro 13 also reacts positively with cells of liver, trachea, tonsil, bladder carcinoma, kidney carcinoma and renal carcinoma.

3.1.3. Finstad

Finstad describes six monoclonal antibodies defining cell surface antigens of human renal cancer that were generated following immunization with renal cancer cells. Of the six, two react with prostate cells and are designated mab S23 and S27. According to the abstract on page 2955, Figure 1 on page 2956, and Table 2 on page 2957 and their accompanying text, mab S23 cross-reacts with cells of the kidney proximal tubule, breast, colon, bladder, transitional cell carcinoma of renal pelvis, colon adenoma, colon adenocarcinoma, lung epidermoid carcinoma, ovarian carcinoma, renal carcinoma, T-cell leukemia and B-cell lymphoma. Mab

S27 cross-reacts with proximal tubule, placental trophoblasts, B-cell leukemia, null cell leukemia, T-cell lymphoma, renal carcinoma, T-cell leukemia and B-cell lymphoma.

3.1.4. Campbell

Campbell is a general review reference on monoclonal antibody technology which describes the general properties and applications of monoclonal antibodies, assay techniques, and selection of animals and cell lines. Of specific interest to the subject application are two statements. The first is found at page 19:

> It is evident that the monoclonal antibodies are not only used for detection of the primary tumor but also for the monitoring of the progress of the disease and of the effects of therapy. It is, however, worth noting that unexpected cross-reactivities may confuse the results. (emphasis added)

On page 23, the following statement is found:

> However, therapy with such powerful reagents is obviously not to be undertaken lightly particularly in light of the unexpected cross-reactivities which can occur with cell surface antigens, all of which would have to be extensively screened. (emphasis added)

Thus, Campbell teaches that cross-reactive monoclonal antibodies are not indicated for therapeutic and diagnostic applications. These quoted sections show that those skilled in the art are aware of the value and utility of specific monoclonal antibodies and the process used to prepare them. When viewing Frankel, Webb and Finstad in the light of Campbell's teaching, it is apparent that Frankel, Webb and Finstad disclose just what Campbell warns against: cross-reacting and non-specific monoclonal antibodies. Certainly, Campbell can not be combined with any of the cited references when it teaches that these references, either individually or

in combination, do not do what Applicant has claimed - the generation of highly specific monoclonal antibodies which recognize prostatic epithelial cells to the exclusion of other organ, tissue, or cell types.

3.1.5. Wright

Wright discloses two monoclonal antibodies, D83.21 and P6.2, that have heterogeneous reactive patterns with some prostate tumors. Mab D83.21 is an IgM antibody that was generated following immunization of mice with DU145 cells. Mab P6.2 is also of the IgM isotype and was generated following immunization of mice with PC-3 cells. On page 5509 in the abstract and on page 5511, Wright discloses that mab D83.21 cross-reacts with bladder carcinomas and normal proximal tubules of kidney. Mab P6.2 has an even broader spectrum of cross-reactivity in that it binds to proximal kidney tubules, breast, bladder, lung, and pancreatic tumors in addition to prostate tumors. Moreover, Wright advocates just the opposite of Applicant's invention when it teaches the following in the abstract on page 5509:

> These results would suggest that a panel of monoclonals will be required to detect the different subpopulations of prostate tumor cells. (emphasis added)

Again on page 5512, Wright teaches away from the use of a single monoclonal antibody when it states:

> The differential reactivity and staining heterogencity observed in the immunoperoxidase-stained prostate tissues would suggest that a panel of well-characterized monoclonal antibodies will be required to detect all the cell types and subpopulations of prostate tumor cells. (emphasis added)

4. Applicant's Invention

In complete contrast to the disclosures of the cited references, Applicant has invented methods for producing and compositions comprising novel monoclonal anti-prostate antibodies with specific binding capabilities useful for cancer immunodiagnosis, prognosis and therapy in humans. The invention provides novel hybridoma-derived monoclonal antibodies which demonstrate a narrow spectrum of organ-specific reactivity with epitopes present specifically and selectively on normal, non-malignant neoplastic and malignant human prostatic epithelium. The monoclonal antibodies do not react specifically with non-prostatic tumors or other non-prostatic tissues. The monoclonal antibodies stain malignant prostatic cells intensely and non-malignant prostatic epithelium weakly. The monoclonal antibodies provided herein also can be used as in vitro immunoserological and immunocytological reagents on body fluids to detect the presence of antigen and/or cells bearing antigen. The monoclonal antibodies permit in vivo non-invasive diagnosis of prostate carcinomas to allow enhanced diagnosis, monitoring and treatment of prostate cancer.

The invention includes a novel process for producing monoclonal antibodies from hybridoma cultures using immunization of mice with whole LNCaP cells or membrane enriched fractions of LNCaP cells [see (1) in claim 16 and related portions of other process claims] and harvesting, from the hybridomas produced, monoclonal antibodies which react specifically with human prostatic cancer cells and normal prostatic cells [see (4)(a) of claim 16 and related portions of other process claims]. Therefore, Applicant has taught, enabled and claimed novel monoclonal antibodies and novel processes to make them.

In contrast, Frankel, Webb, Finstad, and Wright report the isolation of monoclonal antibodies that are not specific for prostatic cells but instead recognize antigens shared by a variety of organ, tissue or cell types. As such, these references can not anticipate the invention disclosed in the present specification.

None of the references teach a process to produce a targeted monoclonal antibody that is specific for a prostate-specific membrane-associated antigen and therefore they are unable to provide monoclonal antibodies useful for diagnosis and therapy of human prostatic carcinomas and can not be used to show any motivation to attempt to use methods described by Campbell for forming such antibodies. Any suggestion that these references provide such a method is merely speculation on what might be possible if indeed a monoclonal antibody could possibly be found for a targeted prostate-specific membrane-associated antigen. Indeed, the references document the failure of skilled artisans to obtain the desired reagent. The Frankel, Webb, Finstad and Wright references do not read on the claimed antibodies or processes for making them. Nor do the Frankel, Webb, Finstad and Wright references predict or suggest the novel monoclonal anti-prostate antibodies with specific binding capabilities useful for cancer immunodiagnosis, prognosis and therapy in humans.

5. The Legal Standard For Anticipation and Obviousness

Anticipation is a narrow and technical attack on patentability; as a consequence, the standards to establish anticipation are strict. Most significantly, the claimed invention must be disclosed within the four corners of a single reference. In re Marshall, 578 F.2d 301, 304, 198 U.S.P.Q. 344, 346 (C.C.P.A. 1978). As Judge Rich stated in Studiengesellschaft Kohle, m.b.H. v. Dart Industries, Inc., 726 F.2d 724, 726-27, 220 U.S.P.Q. 841, 842 (Fed. Cir. 1984):

> The district court correctly stated the law regarding anticipation. It is hornbook law that anticipation must be found in a single reference, device, or process . . . What Dart asked the trial court to do, and what it would have us do on appeal, is to combine the teachings of the [various] references to build an anticipation. That would be contrary to settled law, and the trial court was correct in refusing to do so.

The hornbook law articulated by Judge Rich has not been altered by In re Samour, 571 F.2d 559, 197 U.S.P.Q. 1 (C.C.P.A. 1978). As explained by the Court of Customs and Patent Appeals in In re Marshall, 578 F.2d at 304, 198 U.S.P.Q. at 346:

> Rejections under 35 U.S.C. § 102 are proper only when the claimed subject matter is identically disclosed or described in the prior art. In re Arkley, 455 F.2d 586, 587 59 C.C.P.A. 804, 807, 172 U.S.P.Q. 524, 526 (1972). In other words, to constitute an anticipation, all material elements recited in a claim must be found in one unit of prior art. Soundscriber Corp. v. United States, 360 F.2d 954, 960, 175 Ct.Cl. 644, 148 U.S.P.Q. 298, 301 (1966). This basic principal of patent law has not been disturbed by our recent decision, In re Samour, 571 F.2d 559, 197 U.S.P.Q. 1 (Cust. & Pat.App. 1978).

Applying the legal standard and test of anticipation to the present facts, where no single reference discloses each and every element of Applicant's monoclonal antibodies or methods of producing them as claimed, one must conclude, as a matter of law, that none of the cited references anticipates the claimed subject matter of the present invention. As a result, the Examiner's rejection under 35 U.S.C. § 102(b) must fail.

Examiner also argues that Frankel, Webb and Finstad, alone or combined with Campbell and/or Wright "would have reasonably suggested making the claimed antibodies to one of ordinary skill in the art, making the invention prima facie obvious to one of ordinary skill in the art."

The Examiner's rejection is erroneous as a matter of law because the Examiner has misapplied the test for obviousness under 35 U.S.C. § 103. As articulated by the United States Supreme Court in Graham v. John Deere Co., 383 U.S. 1, 17 (1966), determination of the question of obviousness requires consideration of the scope of the prior art, the level of skill in the pertinent art and differences between the prior art and the claimed subject matter to determine whether, at the time the invention was made, the claimed subject matter would have been obvious. As explained recently by the Court of Appeals for the Federal Circuit in In re Dow Chemical Co., 837 F.2d 469, 473 (Fed. Cir. 1988):

> The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art. Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure. (Citations omitted; emphasis added).

There is no suggestion, much less any indication or expectation of success in any of the references although there is success in Applicant's disclosure. Applicant's success, however, cannot properly be combined with the references to constitute a rejection.

Examiner's contention that the cited references suggest the presently claimed invention is clearly erroneous because the cited references at the very most present nothing more than an invitation to attempt extensive experimentation with no predictable expectation of success. This invitation conforms to the impermissible "obvious to try" standard which is clearly not the standard for obviousness under 35 U.S.C. § 103 as clearly explained by the Court of Appeals for the Federal Circuit and its predecessor the Court of Customs and Patent Appeals. Hybritech Inc. v. Monoclonal Antibodies Inc., 802 F.2d 1367 (Fed. Cir. 1986), cert. denied, 480 U.S. 947, (1987) (lower court's reliance on an "obvious to try" standard is reversible error); accord, In re Geiger, 815 F.2d 686, 688 (Fed. Cir. 1987); N.V. Akzo v. E.I. DuPont de Nemours & Co., 810 F.2d 1148, 1151 (Fed. Cir. 1987) ("Of course, an 'obvious to try' standard is not a legitimate test of patentability"); In re Yates, 663 F.2d 1148, 1151 (Fed. Cir. 1987); In re Goodwin, 576 F.2d 375, 377 (C.C.P.A. 1978) ("This court has consistently refused to recognize 'obvious to try' rejections").

More recently in In re O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988), the court explained situations in which the use of an "obvious to try" standard is particularly inappropriate. The court noted cases in which:

> what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art

gave either no indication of which parameters were critical or no direction to which of many possible choices is likely to be successful.

In applying the legal standard and test of obviousness to the present facts, where no reference suggests, much less discloses Applicant's invention, nor provides any reasonable expectation of success for experiments, and where in fact all references actually document failures to develop Applicant's invention, one must conclude, as a matter of law, that none of the cited references make obvious the claimed subject matter of the present invention. As a result, the Examiner's rejections under 35 U.S.C. § 103 must fail.

6. Conclusion

In light of the above amendment and remarks and the Declarations submitted herewith, attorneys for Applicant submit that the objections to the specification and the rejections under 35 U.S.C. ¶¶ 112, 102, 103 have been obviated and must be withdrawn. Further, attorneys for Applicant submit that the claims as amended are in form for issuance and an early allowance is earnestly requested.

Respectfully submitted,

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